The present invention relates to novel formulations of taxoids for oral administration. More particularly, this invention discloses and claims various semi-solid formulations for the oral administration of taxoids.
FIG. 1
FIG. 2

- □ PEG 4000 50 mg/g
- ▲ PEG 4000 100 mg/g
- ● Vitamine E TPGS 50 mg/g
- ○ Vitamine E TPGS 100 mg/g
- ▲ Gélucire 44/14 50 mg/g
- ● Gélucire 44/14 100 mg/g
FIG. 3
FIG. 4
SEMI-SOLID FORMULATIONS FOR THE ORAL ADMINISTRATION OF TAXOIDS

[0001] This application claims the benefit of priority of European Patent Application No. 03291795.7, filed Jul. 18, 2003, which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] 1. Field of the Invention

[0003] The present invention relates to oral formulations of taxoids.

[0004] 2. Description of the Art

[0005] The taxoids used in the formulations according to the invention are preferably of the general formula (I)

\[
R^1 \text{CO}_{\text{NH}} \text{RO}_{\text{O}} \quad R_1 \text{O}_{\text{O}} \quad R_2 \text{O}_{\text{O}} \quad R_3 \text{O}_{\text{O}} \quad R_4 \text{O}_{\text{O}} \\
\text{O}_{\text{O}} \quad \text{O}_{\text{O}} \quad \text{O}_{\text{O}} \quad \text{O}_{\text{O}} \quad \text{O}_{\text{O}} \\
\text{O}_{\text{O}} \quad \text{O}_{\text{O}} \quad \text{O}_{\text{O}} \quad \text{O}_{\text{O}} \quad \text{O}_{\text{O}}
\]

[0006] wherein

[0007] \( R_1 \) is H, (C_2-C_4)acyl, (C_1-C_3)alkyl,

[0008] \( R_2 \) is OH, alkoxy or \( R_2 \) and \( R_3 \) taken together are methylene,

[0009] \( R_3 \) is CH_3 or \( R_2 \) and \( R_3 \) taken together are methylene,

[0010] \( R_4 \) is OCOCH_3 or OCOOCH_3,

[0011] \( R \) is phenyl, (C_3-C_6)alkoxy or (C_3-C_6)alkenlyoxy, preferably phenyl or tert-butoxy,

[0012] \( R' \) is acyl, preferably phenyl, optionally substituted, (C_2-C_4)alkyl or (C_2-C_4)alkenyl.

[0013] The taxoids used in the formulations according to the invention are for example the taxoids of formula (Ia) to (Ib) below

\[
\text{Formula Ia: (Docetaxel)}
\]

\[
\text{Formula Ib: (Paclitaxel)}
\]
Taxoids of general formula (Ia) to (If) and their applications are known. These taxoids are particularly advantageous for their use as chemotherapeutic agents.

Unfortunately, taxoids are poorly water-soluble compounds. The molecules are slightly lipophilic with a relatively high molecular weight. Up until now taxoids are administered intravenously, in particular, using formulations consisting of PS80 or cremophor at high content. It was the aim of the current invention to develop taxoid formulations for oral administration.

Oral administration of PS80 or cremophor formulations of taxoids led to an extremely low bioavailability in animals probably because of a high metabolism rate, like e.g. dogs. In addition, formulations consisting of a high content of PS80 (e.g. less than 40 mg taxoid per PS80) are not desirable for oral administration because of the potential toxicity of PS80 in contact with the intestinal mucosa. Furthermore, a dose escalation study would not be possible with the expected doses because of the solubility limit and as a consequence the limited PS80 solubilization capacity for taxoids in gastrointestinal fluids. Finally, the pharmaceutical development of a drug dosage form would be a main issue: indeed, the extemporaneous dilution of the PS80 solution with an aqueous medium is not envisageable for the oral administration of a cytotoxic agent.

Numerous documents describe systems suitable for solubilizing and/or enhancing the bioavailability of lipophilic active ingredients. However, the systems tested have so far proved ineffective for the preparation of pharmaceutical compositions containing taxoids which are stable and bioavailable and in which the taxoid can be administered orally at an effective concentration.

WO 95/24893 describes delivery systems for hydrophobic drugs. This application describes compositions comprising a digestible oil, a lipophilic surfactant and a hydrophilic surfactant that are intended for the formulation of hydrophobic active ingredients and for the enhancement of their bioavailability.

WO 99/49848 describes pharmaceutical dosage forms for anticancer drugs, e.g. paclitaxel in which the active drug is formulated as stable self-emulsifying preconcentrate. WO 99/49848 describes compositions comprising an anticancer drug in a carrier system comprising at least one hydrophobic component selected from tri-, di- or monoglycerides, free fatty acids, fatty acid esters or derivatives thereof, and a hydrophilic component selected from hydroxyalkane, dihydroxyalkane or polyethylene glycol (PEG), and comprising at least one surfactant.

EP 0 152 945 B1 describes transparent multi-component systems for pharmaceutical application containing one or several active ingredients in a system composed of an oil component, surfactants, co-surfactant and optionally water.

EP 0 670 715 B1 describes compositions for pharmaceutical use intended to be ingested, able to form a microemulsion, comprising at least an active ingredient, a lipophilic phase, a surfactant, a co-surfactant and a hydrophilic phase of special composition.

EP 0 334 777 B1 describes a micro-emulsion with pharmaceutical use comprising a water-soluble phase and a lipidic phase, comprising at least one surface-active agent based on Polyethylene glycol and at least one co-surfactant based on polyglycerol.

All of the references described herein are incorporated herein by reference in their entirety.

SUMMARY OF THE INVENTION

It has now been found, and that is what constitutes the subject of the present invention, that it is possible to prepare chemically and physically stable formulations of taxoid for oral administration. The present invention relates to a semi-solid formulation for the oral administration of taxoids comprising at least one taxoid and at least one polymeric material that is chosen among Vitamin E TPGS® and Gélucre 44/14®.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1: Taxoid of formula Ib release profile of different formulations at 100 mg/g in simulated gastric medium

FIG. 2: Taxoid of formula Ib release profile of semi-solid formulations at 50 and 100 mg/g in simulated gastric medium

FIG. 3: Particle size of Taxoid of formula Ib formulations in simulated gastric medium

FIG. 4: Particle size of Taxoid of formula Ib formulations leading to droplets ≤50 nm in simulated gastric medium

DETAILED DESCRIPTION OF THE INVENTION

Preferably, the taxoid is of general formula (I):
wherein:

- [0031] \( R_1 \) is H, \((C_2-C_8)\)acyl, \((C_2-C_8)\)alkyl;
- [0032] \( R_2 \) is OH, alkoxy or \( R_2 \) and \( R_3 \) taken together are methylene;
- [0033] \( R_3 \) is CH₃ or \( R_2 \) and \( R_3 \) taken together are methylene;
- [0034] \( R_4 \) is \( \text{OCOCH}_3 \) or \( \text{OCOOCH}_3 \);
- [0035] \( R \) is phenyl, \((C_3-C_8)\)alkoxy or \((C_3-C_8)\)alkenyloxy, preferably phenyl or tert-butoxy; and
- [0036] \( R' \) is aryl, preferably phenyl, optionally substituted or \((C_2-C_8)\)alkyl or \((C_2-C_8)\)alkenyl.

A more preferred taxoid is chosen among compounds of formula (Ia) to (If):
The semi-solid formulation of the invention is particularly suitable for taxoids of formula (Ib) or (Ic).

A convenient semi-solid formulation according to the invention may contain up to 200 mg taxoid per g of polymeric material, more preferably between 50 and 200 mg taxoid per g of polymeric material. Suitable taxoid content may be adapted to the need of a patient, for example taxoid concentration within the polymeric material of e.g. 5 mg/g, 10 mg/g, 20 mg/g, 30 mg/g, 40 mg/g, 50 mg/g, 60 mg/g, 70 mg/g, 80 mg/g, 90 mg/g, 100 mg/g, 150 mg/g or 200 mg/g.

The semi-solid formulations of the invention may optionally further contain at least one additional additive chosen from stabilizing agents, preservatives, agents which make it possible to adjust the viscosity, or agents that can modify the organoleptic properties.

In another aspect the invention concerns a process for preparing a formulation as defined above, wherein there is prepared, where appropriate, the mixture of principal excipients, after heating, for melting the semisolid excipients, and then, if necessary, mixing with the additional additives, and then with the taxoid while stirring in order to obtain a homogeneous mixture.

The strategy has been to obtain a formulation able to enhance taxoid solubilization in aqueous medium by using amphiphilie- and lipid-based formulations able to form a colloidal system (fine emulsion or micellar solution) in vivo.

Among amphiphilic and lipid-based formulations, 3 categories were identified:

Amphiphilic polymers (micelle or emulsion formation)

Phospholipids (lipidic vesicles formation)

SMES (self-microemulsifying systems): oil+ surfactant+co-surfactant (microemulsion formation)

After a first selection of proper excipients (in terms of safety and developability), the solubility of taxoids in the excipient was the first screening step for the choice of the excipient and the selection of the prototypes. Then, the prototypes (liquid or semi-solid) were manufactured, and characterized in terms of in vitro behavior in simulated GI media and chemical stability. Finally, the physical properties and stability of the semi-solid prototypes have been investigated.

Different categories of excipients described in the literature as components of amphiphilic and lipid-based formulations have been tested for the solubility of taxoids:

1. Oils (medium-chain triglycerides, fatty acids, . . .)
2. Amphiphilic surfactants with hydrophilic character (HLB>10) (PEO sorbitan fatty acids, castor oil ethoxylates, fatty acid ethoxylates.)
3. Amphiphilic surfactants with lipophilic character (HLB<10) (glycerides of fatty acids: glyceryl olate/linolate, oleyl macrogol glycerides; derivatives of propylene glycol: PG caprylate/linolate)
4. Phospholipids (lecithins)
5. Hydrophilic solvents (PEG 400, . . .)

All the selected excipients are described as safe for oral administration, and they are developable (alone or as mixture) as pharmaceutical dosage form (soft or hard capsule).

The chemical composition of the selected excipients in liquid form at room temperature, as well as the solubility of taxoid of formula Ib, are reported in table 1 below.

<table>
<thead>
<tr>
<th>Commercial name</th>
<th>Chemical description</th>
<th>Solubility (mg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miglyol 812N</td>
<td>caprylic/capric triglyceride</td>
<td>65</td>
</tr>
<tr>
<td>Soybean oil</td>
<td>glycerides (linoleic acid 50–57%)</td>
<td>16</td>
</tr>
<tr>
<td>Amphiphilic surfactants with lipophilic character (HLB ≤ 10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crossential O94</td>
<td>Oleic acid</td>
<td>37</td>
</tr>
<tr>
<td>Labrafil M1944 CS</td>
<td>oleyl macrogol-6-glycerides</td>
<td>52</td>
</tr>
<tr>
<td>Edonor CS 98–100</td>
<td>Caprylic acid</td>
<td>138</td>
</tr>
<tr>
<td>Pluronic dioestere</td>
<td></td>
<td>22</td>
</tr>
<tr>
<td>Pecol</td>
<td>Glycerol monostearate</td>
<td>138</td>
</tr>
<tr>
<td>Lanoglycol 129</td>
<td>PG monooleate</td>
<td>129</td>
</tr>
<tr>
<td>Capryol 90</td>
<td>Polyethylene glycol monooleate</td>
<td>281</td>
</tr>
<tr>
<td>Macrolin 35-1</td>
<td>Glycerol linolate</td>
<td>129</td>
</tr>
<tr>
<td>Pluronic CC407</td>
<td>Poliglycerol 6 oleate</td>
<td>42</td>
</tr>
<tr>
<td>Amphiphilic surfactants with hydrophilic character (HLB &gt; 10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS 80 V0</td>
<td>POE monostearate</td>
<td>144</td>
</tr>
<tr>
<td>PS 80 V0, pH 6</td>
<td>POE monostearate</td>
<td>135</td>
</tr>
<tr>
<td>Cremophor EL</td>
<td>POE hydrogenated castor oil</td>
<td>94</td>
</tr>
<tr>
<td>Labrosol</td>
<td>Caprylicpropyl macrogol-8 glycerides</td>
<td>244</td>
</tr>
</tbody>
</table>

Solvents, cosolvents

Ethanol
HBP cyclodextrin
Transcutol
PEG 400

250
0.28
197
121

205/0070496 A1
Mar. 31, 2005
TABLE 1-continued

<table>
<thead>
<tr>
<th>Commercial name</th>
<th>Chemical description</th>
<th>Solubility (mg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosal 50 SA</td>
<td>Phosphatidylcholine 50 ± 3% in alcohol, suflower oil, glyceryl stearate, coconut oil and ascorbyl palmitate</td>
<td>97</td>
</tr>
<tr>
<td>Phosal 75 SA</td>
<td>Phosphatidylcholine 75 ± 3% in alcohol, suflower oil, glyceryl stearate, coconut oil and ascorbyl palmitate</td>
<td>122</td>
</tr>
<tr>
<td>Phosal 50 PG</td>
<td>Phosphatidylcholine ≥ 50% in propylene glycol</td>
<td>27</td>
</tr>
</tbody>
</table>

The following table 2 reports the chemical composition of the selected excipients in semi-solid form at room temperature, as well as the solubility of a taxoid of formula Ib. Excipients had been previously melted up to 70°C for drug dissolution.

TABLE 2

<table>
<thead>
<tr>
<th>Commercial name</th>
<th>Chemical description</th>
<th>Solubility (mg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inwiorc 988</td>
<td>Glyceryl mono-diacyl glyceride</td>
<td>283</td>
</tr>
<tr>
<td>Phospholipid</td>
<td>Hydrophilic surfactants and amphiphilic surfactants with hydrophilic character (HLB &gt; 10)</td>
<td>73</td>
</tr>
<tr>
<td>PEG 4000</td>
<td>polyethylene glycol 1500</td>
<td>&gt;50*</td>
</tr>
<tr>
<td>Gelsecre 44/14</td>
<td>lauryl macrogol-32 glycerides</td>
<td>96</td>
</tr>
<tr>
<td>Vitamin E TPGS</td>
<td>co-tocopherol PEG succinate</td>
<td>73</td>
</tr>
<tr>
<td>Myrij 45</td>
<td>POE stearate</td>
<td>128</td>
</tr>
<tr>
<td>Phospholipids</td>
<td></td>
<td>Not done</td>
</tr>
</tbody>
</table>

The solubility of taxoid of formula Ib at room temperature has been determined by X-ray diffraction.

Taking into account the solubility of a taxoid of formula Ib, for the 3 categories of drug delivery systems the following excipients were retained:

- Vitamin E TPGS for micelle formation
- Phosal 75SA and Phospholipon 90H for lipidic vesicle formation
- Labrasol and Gelsecre 44/14 for emulsion formation

Microemulsion formation: as surfactant Myrij 45, PS80, Cremophor EL, Labrasol; as co-surfactant: Maisine, Capryol 90, Pecool, Laurogelyol 90, Imwitor 988; as oil: Miglyol 812N, Edcno.

For the first 3 categories, the excipients were formulated as binary systems with the drug, at the following concentrations:

- Vitamin E TPGS (semi-solid matrix): 50, 100 mg/g formulation
- Phosal 75SA (solution): 100 mg/g formulation
- Phospholipon 90H (solid powder): 50, 100 mg/g formulation
- Gelsecre 44/14 (semi-solid matrix): 50, 100 mg/g formulation
- Labrasol (solution): 50, 100, 200 mg/g formulation

For the SMES category (3-components system), a first screening of the excipients as oil, surfactant (HLB>10) and co-surfactant (HLB<10), combined together at different ratios without the presence of the active, was necessary for identifying the formulations able to form a microemulsion (droplet size <50 nm) after infinite dilution with water. With this screening the following SMES were identified:

- Cremophor EL/Maisine/Miglyol 812N at 50 mg/g
- Cremophor EL/Lauroglycol 90/Miglyol 812N at 50 mg/g
- Cremophor EL/Capryol 90/Miglyol 812N at 50 mg/g
- Cremophor EL/Pecool/Miglyol 812N at 50 mg/g
- Cremophor EL/Imwitor 988/Miglyol 812N at 50 mg/g

The ratio between the excipients in the retained formulations was as follows: ratio surfactant to co-surfactant 3:1 and with oil concentration of 20%.

It is understood that the dosage may vary according to the degree or the nature of the condition to be treated. Thus, the quantity of active product in a composition according to the invention will be determined such that a suitable dosage can be prescribed. As a result, the quantity of taxoids varies as a function of its solubility in the mixture and also as a function of the appropriate dosage for the treatment of patients. Preferably, care should be taken not to load more than 10% w/w of taxoid drug so as to avoid microemulsion destabilization to occur.

In humans, it is understood that, to choose the most appropriate daily dosage, there should be taken into account the weight of the patient, his general state of health, his age and all factors which may influence the efficacy of the treatment. Preferably, the compositions are prepared such that a unit dose contains from 0.1 to 50 mg of active product.

In the alternative, where a second active ingredient is introduced, the compositions may comprise 0.2 to 50 mg. However, this quantity may optionally be lower and may vary from 0.2 to 10 mg.

When the composition further comprises certain additional additives, the latter may be stabilizing agents, preservatives, agents which make it possible to adjust the viscosity, or agents that can modify, for example, the organoleptic properties.

The stabilizing agents may be, for example, antioxidants chosen in particular from tocopherol, ascorbyl palmitate, BHT (butyl hydroxytoluene), BHA (butyl hydroxyanisole), propyl gallate or malic acid for example.
The preservatives may, by way of example, be chosen from sodium metabisulfite, propylene glycol, ethanol or glycerin.

Among the agents capable of adjusting the viscosity, there may be mentioned, for example, lecithins, phospholipids, propylene glycol alginate, sodium alginate or glycerin.

The agents capable of modifying the organoleptic properties of the composition are, by way of example, malic acid, fumaric acid, glycerin, vanillin or menthol.

When such additives are used, the latter may constitute from 0.001% to 5% by weight of the total composition.

According to the invention, the pharmaceutical composition may be obtained by mixing, where appropriate, the principal excipients (after heating for melting the semi-solid excipients), and then, if necessary, mixing with the additional additives, followed by the addition of the taxoid and maintaining stirred in order to obtain a homogeneous mixture.

The compositions according to the invention may be provided in the semi-pasty state.

They are particularly suitable for presentation in the form of hard gelatin capsules or soft gelatin capsules, or in the form of an oral solution.

The compositions according to the invention are particularly advantageous because of their good stability, both physically and chemically, and the enhancement of the bioavailability which they offer upon oral administration of taxoids.

The following examples, given without limitation, illustrate formulations according to the present invention.

**EXAMPLES**

**Example 1**

**Preparation of Prototypes**

**Materials**

- Taxoid of formula Ib
- Miglyol 812N (Condea Vista Company, Cranford, N.J., USA)
- Labrasol (Gattefossé, Saint Priest, F)
- Gelucire 44/14 (Gattefossé, Saint Priest, F)
- Vitamin E-TPGS (Eastman Chemical, Anglosey, UK)
- Cremophor EL (BASF AG, Ludwigshafen, DE)
- Capryol 90 (Gattefossé, Saint Priest, F)
- Lauroglycol 90 (Gattefossé, Saint Priest, F)
- Pcecel (Gattefossé, Saint Priest, F)
- Maisine 35-1 (Gattefossé, Saint Priest, F)
- Inwitor 988 (Condea Vista Company, Cranford, N.J., USA)

**Formulations**

- Phos 80
- Capryol 90
- Labrasol
- Phos 75 SA
- Gelucire 44/14
- Vitamin E-TPGS
- Cremophor EL-Miglyol 812N-Pcecel
- Cremophor EL-Miglyol 812N-Maisine
- Cremophor EL-Miglyol 812N-Lauroglycol 90
- Cremophor EL-Miglyol 812N-Capryol 90
- Cremophor EL-Miglyol 812N-Inwitor 988
- Phospholipon 90 H
- Phospholipon 90 H

**Table 3**

<table>
<thead>
<tr>
<th>Prototype</th>
<th>DRUG CONCENTRATION (mg/g formulation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS 80</td>
<td>100</td>
</tr>
<tr>
<td>Capryol 90</td>
<td>250</td>
</tr>
<tr>
<td>Labrasol</td>
<td>100</td>
</tr>
<tr>
<td>Labrasol</td>
<td>200</td>
</tr>
<tr>
<td>Phos 75 SA</td>
<td>100</td>
</tr>
<tr>
<td>Gelucire 44/14</td>
<td>80</td>
</tr>
<tr>
<td>Gelucire 44/14</td>
<td>100</td>
</tr>
<tr>
<td>Vitamin E-TPGS</td>
<td>60</td>
</tr>
<tr>
<td>Cremophor EL-Miglyol 812N-Pcecel</td>
<td>50</td>
</tr>
<tr>
<td>Cremophor EL-Miglyol 812N-Maisine</td>
<td>50</td>
</tr>
<tr>
<td>Cremophor EL-Miglyol 812N-Lauroglycol 90</td>
<td>50</td>
</tr>
<tr>
<td>Cremophor EL-Miglyol 812N-Capryol 90</td>
<td>50</td>
</tr>
<tr>
<td>Cremophor EL-Miglyol 812N-Inwitor 988</td>
<td>50</td>
</tr>
<tr>
<td>Phospholipon 90 H</td>
<td>50</td>
</tr>
<tr>
<td>Phospholipon 90 H</td>
<td>100</td>
</tr>
</tbody>
</table>

All the formulations are stable for 3 months at 40°C under 75% RH, except the SMES formulations. Indeed, the SMES are stable for 1 month at 25°C, whereas at 40°C an impurity of taxoid of formula Ib (hydrolysis) appears (λ<sub>max</sub> at λ<sub>max</sub>, depending on the nature of the co-surfactant). The 3 months analysis of the sample allowed to evaluate if this impurity increase was critical: after 3 months, an increase of taxoid of formula Ib impurity content was noticed. The SMES is stable at 5°C during 7 months.
Example 2

[0112] In Vitro Behavior in Simulated GI Media (GI= Gastro Intestinal Tract)

[0113] Release profiles after incubation in simulated GI media

[0114] 2.1 Composition of the Simulated Fluids

[0115] The following simulated media were selected for the present experiment:

[0116] Gastric medium USP, pH 1.2


<table>
<thead>
<tr>
<th>TABLE 4</th>
<th>Composition of the simulated gastro-intestinal media</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastric medium (G)</strong></td>
<td></td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>2 g</td>
</tr>
<tr>
<td>Hydrogen chloride 1N</td>
<td>100 ml approximately</td>
</tr>
<tr>
<td>Demineralised water</td>
<td>qsp 1000 ml</td>
</tr>
<tr>
<td><strong>Fasted intestinal medium (Fussill)</strong></td>
<td>For 500 ml</td>
</tr>
<tr>
<td>Potassium hydrogenophosphate</td>
<td>0.029 M 1.97 g</td>
</tr>
<tr>
<td>Sodium hydroxide</td>
<td>qsp pH 6.8</td>
</tr>
<tr>
<td>Sodium Taurocholate</td>
<td>5 mM 1.34 g</td>
</tr>
<tr>
<td>Lecithin (Phospholipon 90G)</td>
<td>1.5 mM 0.58 g</td>
</tr>
<tr>
<td>Potassium chloride</td>
<td>0.22 M 8.2 g</td>
</tr>
<tr>
<td>Demineralised water</td>
<td>qsp 11 qsp 500 ml</td>
</tr>
<tr>
<td>Fed intestinal medium (Fussill)</td>
<td>For 500 ml</td>
</tr>
<tr>
<td>Acetic acid</td>
<td>0.144 M 4.33 g</td>
</tr>
<tr>
<td>Sodium hydroxide</td>
<td>qsp pH 5</td>
</tr>
<tr>
<td>Sodium Taurocholate</td>
<td>15 mM 4.63 g</td>
</tr>
<tr>
<td>Lecithin (Phospholipon 90G)</td>
<td>4 mM 1.55 g</td>
</tr>
<tr>
<td>Potassium chloride</td>
<td>0.19 M 7.08 g</td>
</tr>
<tr>
<td>Demineralised water</td>
<td>qsp 11 qsp 500 ml</td>
</tr>
</tbody>
</table>

[0119] 2.2 Experimental Conditions

[0120] In a first step of experiments, the formulations (100 mg drug/g formulation, 500 mg formulation in a hard gelatin capsule) were diluted 1:500 in the gastric medium (1 capsule/250 mL), and then incubated 2 hours at 37°C. under stirring (50 rpm) in a USP standard dissolution apparatus.

[0121] The same experiment has been carried out in gastric medium with 2 capsules loaded with less concentrated formulations (50 mg drug/g formulation), in order to study the effect of the drug/excipient and excipient/medium ratio on the release profile. In a second step of experiments, a first incubation of 1 hour in gastric medium was followed by 2 hours incubation in fasted intestinal or fed intestinal medium, in order to simulate the gastric emptying process.

[0122] Samples were taken after 5-15-30-60 min and 2 h. The drug concentration was determined by HPLC after centrifugation (6000 rpm, 10 min). Homogeneity of the medium was evaluated by sampling bottom, medium and top of the vessel.

[0123] 2.3 Results

[0124] Drug release profiles in gastric medium of formulations at 100 mg/g are shown in the FIG. 1.

[0125] Compared to the PS80 formulation (evaluated as reference), only the formulation composed of Vitamin E TPGS allowed improvement of the in vitro solubilization of taxoid of formula Ib (80% of drug solubilized) by 2 hours.

[0126] Concerning the profiles obtained with the other formulations data from Phosal and Gelucire are not very representative, since these formulations led to the formation of a very heterogeneous mixture after incubation. For Gelucire 44/14, the disintegration of the semi-sld matrix occurred only partially, not allowing the dispersion in the simulated gastric medium. The Labrasol formulation led to the formation of a very homogeneous emulsion with the medium, despite the low amount of drug recovered after centrifugation (see release profile), suggesting that for a coarse emulsion the centrifugation (determining the collapse of the emulsion) could sub-estimate its in vitro performance. The experiment with Phospholipon 90H was stopped (no data collection) since the powder floating did not allow the formation of a homogeneous suspension.

[0127] The comparison of the drug release profiles of semi-solid formulations (Gelucire, Vitamin E TPGS and PEG 4000) at 50 et 100 mg/g (FIG. 2; the profiles related to Vitamin E TPGS and Gelucire at 100 mg/g are the same already reported in FIG. 1) shows that Vitamin E TPGS exhibited the highest solubilization properties, with a release of 80% for the 100 mg/g dosage and up to 100% for the 50 mg/g dosage. The Gelucire formulation at 50 mg/g allowed the solubilization of about 80% of drug, contrarily to the 100 mg/g dosage, as described previously. Finally, the hydrophilic PEG 4000 confirmed, as expected, the inability to solubilize a hydrophobic drug in an aqueous medium.

Example 3

[0128] Particle Size Analysis after Incubation in Gastric Medium (USP)

[0129] The aim of this part of the study was to evaluate, by particle size measurement, the colloidal stability and the self-emulsifying properties of the emulsion/microemulsion/micellar solution of taxoid of formula Ib formulations after incubation in the gastric medium.

[0130] 3.1 Experimental Conditions

[0131] The formulations (concentration 100 mg drug/g formulation, 100 mg formulation) were diluted 1:500 in the gastric medium (50 mL), then incubated 2 hours at 37°C. under mechanical stirring (300 rpm).

[0132] The sample was diluted immediately with water for size measurement or filtered onto 2 μm if necessary. The filtration allowed to retain oil droplets ≥2 μm, as well as drug crystals ≥2 μm, in order to allow the particle size measurement by QELS (quasi-elastic light scattering) (Nanosizer N4+, Beckmann-Coulter).

[0133] 3.2 Results

[0134] As shown in the FIGS. 3 and 4, a particle size <50 nm was obtained only in the case of the formulations with active concentration of 50 mg/g, the 5 microemulsions (nevertheless their composition), Gelucire (after 2 μm filtration) and Vitamin E TPGS.

[0135] The results suggest using the formulations able to form small and monodispense droplets in gastric medium in order to have a better performance in vivo. Further experiments in simulated intestinal media should be performed in
order to evaluate the effect of biliary salts on the size and colloidal stability of the formulations.

[0136] 3.3 Preliminary Conclusions on the Evaluation of Taxoid of Formula Ib Formulations

[0137] All the results concerning the in vitro behavior in simulated GI fluids of the formulations for oral administration of taxoid of formula Ib, as well as the chemical stability in accelerated conditions, are summarized in the tables below.

**TABLE 5**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Chemical Stability</th>
<th>Droplet size in vitro (2 h at 37°C in gastric medium)</th>
<th>Homogeneity in vitro (2 h at 37°C in gastric medium)</th>
<th>% Released drug in vitro after 2 h in gastric medium</th>
<th>% Released drug in vitro after 1 h gastric + 2 h Fassif</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E TPGS</td>
<td>&gt;3 months at 40°C, 75% RH</td>
<td>16 nm</td>
<td>Good</td>
<td>100%</td>
<td>Not done</td>
</tr>
<tr>
<td>Gelucire 44/14</td>
<td>&gt;3 months at 40°C, 75% RH (after filtration)</td>
<td>45 nm</td>
<td>Good</td>
<td>79%</td>
<td>&gt;60%</td>
</tr>
</tbody>
</table>

**TABLE 6**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Chemical Stability</th>
<th>Droplet size in vitro (2 h at 37°C in gastric medium)</th>
<th>Homogeneity in vitro (2 h at 37°C in gastric medium)</th>
<th>% Released drug in vitro after 2 h in gastric medium</th>
<th>% Released drug in vitro after 1 h gastric + 2 h Fassif</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E TPGS</td>
<td>&gt;3 months at 40°C, 75% RH</td>
<td>335 nm</td>
<td>Good</td>
<td>82-84%</td>
<td>60%</td>
</tr>
<tr>
<td>Gelucire 44/14</td>
<td>&gt;3 months at 40°C, 75% RH (after filtration)</td>
<td>118 nm</td>
<td>Bad</td>
<td>Not determined</td>
<td>Not determined</td>
</tr>
</tbody>
</table>

[0139] Gelucire leads to a heterogeneous emulsion with the GI media, so it was discarded at this concentration. Thus, at 100 mg/g, only Vitamin E TPGS formulation exhibited a promising behavior (in terms of release profile and droplet size).

Example 4

[0140] Physical Characterization and Stability of Semi-Solid Matrices

[0141] 4.1 Experimental Methods

[0142] X-RAY POWDER DIFFRACTION (XRPD)

[0143] The analyses are carried out on a Siemens-Brucker D5000 Matic diffractometer, using the parafocusing Bragg-Brentano (0-20)-type geometry. If enough of the product is available, the powder is deposited on a concave aluminium sample holder. Otherwise a thin layer of the product is deposited on a single-crystalline silicon wafer, cut out according to the (510) crystallographic orientation that impedes any Bragg reflection (by ensuring the systematic extinction of the corresponding diffraction band). A cobalt anticathode tube (40 kV/30 mA) gives an iron-filtered incident beam. Two radiations are emitted: CoKα1 (𝜆=1.7890 Å) and CoKα2 (𝜆=1.7929 Å). A 50 M multi-channel Braun linear detector completes the setup. It has a 10°-wide detection window in angle 2θ. Diagrams were recorded in the following conditions: a 1.5 to 50.0 degree scan in angle 2θ, 10 to 50 seconds’ counting time per degree in 20 degrees.
a solubilized semi-solid formulation or polymorphism in a dispersed one.

Two semi-solid formulations (a 60 mg/g VitaminE-TPGS one and a 80 mg/g Gelucire one) were evaluated after one month at 30° C./60% RH or at 40° C./75% RH. Both formulations were mostly solubilized after manufacturing and no recrystallization was observed after one month. We can anticipate that both 50 mg/g formulations are physically stable for at least one month.

4.3 Conclusions and Further Studies

<table>
<thead>
<tr>
<th>TABLE 7</th>
<th>Comparative properties of the recommended formulations according to the selection criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>FORMULATION</td>
<td>TPGS</td>
</tr>
<tr>
<td>Safety excipients</td>
<td>Yes</td>
</tr>
<tr>
<td>Registrability excipients</td>
<td>Yes</td>
</tr>
<tr>
<td>Developability/registrability formulation</td>
<td>Yes</td>
</tr>
<tr>
<td>Conc. &gt;50 mg/g</td>
<td>Yes (up to 100)</td>
</tr>
<tr>
<td>Chemical Stability 1 month</td>
<td>40° C./75% RH</td>
</tr>
<tr>
<td>Solubilization in GI media</td>
<td>Very good</td>
</tr>
<tr>
<td>Fine droplet size (GI media)</td>
<td>Yes (16 mm)</td>
</tr>
<tr>
<td>Physical Stability 1 month</td>
<td>40° C./75% RH</td>
</tr>
</tbody>
</table>

What is claimed is:

1. A semi-solid formulation for the oral administration of taxoids comprising at least one taxoid and at least one polymeric material chosen from Vitamin E TPGS® and Gelucire 44/14®.

2. The semi-solid formulation as set forth in claim 1, wherein the taxoid is a taxoid of general formula (I):

3. The semi-solid formulation as set forth in claim 2, wherein R is t-butoxy and R' is phenyl, optionally substituted.

4. The semi-solid formulation as set forth in claim 2, wherein the taxoid is chosen from compounds of formula (Ia) to (Ib):
5. The semi-solid formulation as set forth in claim 4, wherein the taxoid is chosen from compounds of formula (Ib) and (Ic).

6. The semi-solid formulation as set forth in claim 1, wherein the formulation contains up to about 200 mg taxoid per g of polymeric material.

7. The semi-solid formulation as set forth in claim 2, wherein the formulation contains up to about 200 mg taxoid per g of polymeric material.

8. The semi-solid formulation as set forth in claim 4, wherein the formulation contains up to about 200 mg taxoid per g of polymeric material.

9. The semi-solid formulation as set forth in claim 1, wherein the formulation contains from about 5 mg to about 100 mg of taxoid per g of polymeric material.

10. The semi-solid formulation as set forth in claim 2, wherein the formulation contains from about 5 mg to about 100 mg of taxoid per g of polymeric material.

11. The semi-solid formulation as set forth in claim 4, wherein the formulation contains from about 5 mg to about 100 mg of taxoid per g of polymeric material.

12. The semi-solid formulation as set forth in claim 1, further comprising at least one additional additive chosen from stabilizing agents, preservatives, agents which make it possible to adjust the viscosity, or agents that can modify the organoleptic properties.

13. The semi-solid formulation as set forth in claim 2, further comprising at least one additional additive chosen from stabilizing agents, preservatives, agents which make it possible to adjust the viscosity, or agents that can modify the organoleptic properties.

14. The semi-solid formulation as set forth in claim 4, further comprising at least one additional additive chosen from stabilizing agents, preservatives, agents which make it possible to adjust the viscosity, or agents that can modify the organoleptic properties.

15. A semi-solid formulation for the oral administration of taxoids comprising at least one taxoid and at least one polymeric material chosen from Vitamin E TPGS® and Gélucire 44/14®, wherein the taxoid is of general formula (I):

\[
\text{(I)}
\]

wherein:

\[R_1 = \text{H, (C}_2\text{-C}_6\text{)acyl or (C}_1\text{-C}_6\text{)alkyl;}
\]

\[R_2 = \text{OH or alkoxy;}
\]

\[R_3 = \text{CH}_2\text{ or } R_2 \text{ and } R_3 \text{ taken together are methylene;}
\]

\[R_4 = \text{OCOCH}_3\text{ or OCOOCH}_3\text{;}
\]

\[R = \text{phenyl, (C}_3\text{-C}_4\text{)alkoxy or (C}_3\text{-C}_4\text{)alkenylxyl; and}
\]
R' is aryl, optionally substituted, (C₂-C₄)alkyl or (C₅-C₇)alkenyl.

16. The semi-solid formulation as set forth in claim 15, wherein the taxoid is chosen from compounds of formula (Ia) to (If):

-continued
17. The semi-solid formulation as set forth in claim 16, wherein the taxoid is chosen from compounds of formula (Ib) and (Ic).

18. A semi-solid formulation for the oral administration of a taxoid comprising at least one taxoid and at least one polymeric material chosen from Vitamin E TPGS® and Géluirc 44/14®, wherein the taxoid is of formula (Ib) or (Ic):

19. The semi-solid formulation as set forth in claim 18, wherein the taxoid is of formula (Ib).

20. The semi-solid formulation as set forth in claim 18, wherein the taxoid is of formula (Ic).

21. A process for the preparation of a formulation as set forth in claim 1 comprising:

- mixing the principal excipients while stirring to form a mixture, and heating optionally, the mixture for melting the semisolid excipients;
- mixing optionally with the additional additives, and the taxoid; and
- maintaining stirring in order to obtain a homogeneous mixture.

* * * * *